REMARKS

Claim 70 has been cancelled. Claims 1, 16, 19-22, 25, 28, 29, 31, 36, 37, 39, 40, 43-46, 49, 52, 56-59, 62, 68 and 69 have been amended. New claims 71-88 have been added.

The amendment to claims 1, 29 and 52 is supported by cancelled claim 70 and by the specification, at least at paragraphs 00113 and 00118.

The amendments to claims 16 and 31 correct inadvertent typographical errors.

The amendments to claims 19, 20, 43, 44, 56 and 57 are supported by the specification, at least at paragraph 0047. The amendments to claims 21, 25, 45, 49, 58 and 62 are supported by the specification, at least at paragraph 0052.

Claims 22, 46 and 59 have been amended to depend directly from claims 1, 29 or 52, respectively. These claims also have been amended to include language consistent with their respective amended independent claims.

Claim 28 has been amended to be consistent with amended claim 1.

Claims 29, 36, 37, 39 and 40 have been amended to provide correct antecedent basis regarding the term "emulsion".

Claim 68 has been amended to provide language consistent with claim 1, and is supported by the specification, at least at Example 37, pages 33-34. Claim 69 has been amended to provide language consistent with claim 1.

New claims 71-76 and 79-81 are supported by cancelled claim 70, and by supported by the specification, at least at Examples 31-36, pages 29-33. New claims 77 and 82 are supported by claim 68, and new claims 78 and 83 are supported by claim 69.

New claim 84 is supported by the specification, at least at Example 32, page 30. New claims 85-88 are supported by the specification, at least at Example 33, pages 30-31.

No new matter has been added.

Claims 1-64, 68, 69 and 71-88 are pending.

INTERVIEW SUMMARY

Applicants would like to thank Examiners Teller and Kosar for the helpful discussion with Applicants' representatives on October 20, 2010. During this discussion, independent claim 1 was reviewed with respect to the references of record.

REQUEST FOR RECONSIDERATION

Independent claims 1, 29 and 52 have been amended to remove the qualifier "inert to propofol", and instead to recite a description of the protection of propofol in a composition within a container having a closure. In paragraph 00118 of the specification, successful protection of propofol in a composition is described as a loss in propofol potency that is at most marginal (i.e. less than 7%) after the composition is subjected to a specific agitation protocol. The procedure for determining this loss of propofol potency is described at paragraph 00113, lines 1-10 as measuring propofol concentration (w/v) in the composition using HPLC assays before and after the composition is subjected to the agitation protocol. Thus, the independent claims as amended describe the protection of propofol from degradation by reciting that when a claimed composition of propofol in a container sealed with a closure is agitated at a frequency of 300-400 cycles/minute for 16 hours at room temperature, the composition maintains a propofol concentration (w/v) measured by HPLC that is at least 93% of the starting concentration (w/v) of the propofol.

Claims 1-64, 68 and 69 have been rejected as obvious over U.S. Patent No. 6,399,087 to Zhang et al. (Zhang) in view of U.S. Patent No. 6,576,245 to Lundgren et al. (Lundgren) and Sautou-Miranda, *Int. J. Pharm.* **130**, 251-255, 1996 (Sautou-Miranda).

Independent claim 1 is not obvious over the cited references, alone or in combination. The claim as amended recites a composition that includes less than 10% by weight solvent for propofol and in which the propofol is protected from degradation, where the protection is determined by the agitation / concentration measurement procedure recited in the claim. One of ordinary skill in the art would not have had a reasonable expectation of success in combining the propofol compositions of Zhang with the containers of Lundgren to provide a composition in a container in which the propofol

is protected as claimed. Zhang is silent with respect to a need to protect propofol in compositions having less than 10% oil. Lundgren's teaching regarding the selection of a closure for containers of peptide-based therapeutic formulations cannot be extended to reasonably predict success in protecting propofol in compositions such as those of Zhang. In addition, Zhang teaches away from the compositions disclosed in Sautou-Miranda. Thus, it would not have been obvious to combine Zhang with Lundgren and/or Sautou-Miranda to provide a propofol composition in a container in which the propofol is protected as claimed.

Independent claim 29 is not obvious over the cited references. Claim 29 recites an emulsion including an oil phase that includes propofol, an aqueous phase, and a stabilizing layer for the oil phase that includes a surfactant and a protein. The cited references, alone or in combination, do not disclose or suggest an emulsion having a stabilizing layer that includes a surfactant and a protein. Thus, the combination of the references would not provide each and every element of claim 29.

Independent claim 52 is not obvious over the cited references. Claim 52 recites microdroplets and an injectable carrier, where the microdroplets contain propofol spheres surrounded by a layer containing a phospholipid but without any oils that can support bacterial growth. The cited references, alone or in combination, do not disclose or suggest microdroplets containing propofol as claimed. Thus, the combination of the references would not provide each and every element of claim 52.

CLAIM 1 IS NOT OBVIOUS OVER ZHANG AND LUNDGREN

Independent claim 1 is not obvious over Zhang in view of Lundgren. The claim as amended recites a composition that includes from 0.5 to 10% propofol by weight and less than 10% by weight solvent for propofol, and in which the propofol is protected from degradation as determined by the recited agitation / concentration measurement procedure. Zhang teaches only low oil propofol formulations, whereas Lundgren teaches only the selection of closures for containers of peptide-based formulations. Thus, one of ordinary skill in the art would not have had a reasonable expectation of success in

combining the propofol compositions of Zhang with the containers of Lundgren to provide a composition in a container in which the propofol is protected as recited in claim 1.

Zhang is silent with respect to a need to protect propofol in compositions having less than 10% by weight solvent for propofol. Zhang discloses propofol formulations having a reduced amount of soybean oil triglycerides, a reduced amount of lecithin surfactant, and no preservatives (col. 3, lines 17-27). Compared to the formulation sold commercially as DIPRIVAN®, which contains 10% (w/v) soybean oil, 1.2% (w/v) egg lecithin surfactant, and EDTA preservative (col. 1, lines 57-63), the low oil formulations of Zhang are at least as effective in preventing microbial growth (col. 8, lines 14-18). Zhang does not disclose rates of degradation of propofol in the low oil formulations. Thus, while Zhang discloses propofol formulations that may be consistent with lines 5-6 of Applicants' claim 1, the reference as a whole would not have motivated one of skill in the art to investigate different containers that could provide protection for propofol in such formulations.

Lundgren's teaching regarding the protection of peptide therapeutics cannot be extended to reasonably predict its success in protecting propofol in low oil compositions. Lundgren discloses formulations of melagatran, a peptide-based thrombin inhibitor (col. 2, lines 12-16). Melagatran is soluble in water (col. 2, lines 17-18 and 65), whereas propofol is a water-insoluble oil (Zhang, col. 1, line 22). In the PubChem compound summary attached as **Exhibit A**, melagatran is listed as an anticoagulant having a molecular weight of 429.51 grams per mole (g/mol), and containing 5 hydrogen-bond donors and 5 hydrogen-bond acceptors. In contrast, in the PubChem compound summary attached as **Exhibit B**, propofol is an anesthetic having a molecular weight (178.27 g/mol) that is less than half of that of melagatran, and includes only 1 hydrogen-bond donor and 1 hydrogen-bond acceptor. These documents and the references of record establish that the active ingredient of Lundgren is unrelated to propofol at least with respect to molecular weight, chemical structure, chemical reactivity, solubility and therapeutic use. Thus, Lundgren's teachings regarding protection of an active ingredient is limited to the protection of melagatran and similar water soluble, peptide-based thrombin inhibitors, and cannot be reasonably extended to provide a teaching regarding protection of propofol.

In addition, Lundgren's teaching regarding the selection of closure materials cannot be extended beyond a preference for bromobutyl rubber. Lundgren discloses formulations of melagatran that are stored in syringes fitted with plungers containing either chlorobutyl rubber or bromobutyl rubber (Examples 1 and 3). When stored in the syringes for 3 months or 6 months at room temperature (25 °C), the melagatran in the formulations degraded less when the plunger contained bromobutyl rubber than when the plunger contained chlorobutyl rubber, as shown in the results listed in the table spanning columns 3-4. Lundgren does not offer an explanation for the performance difference between the two types of rubber and thus does not teach principles that could be applied to other compositions. Moreover, the overall degradation of melagatran at 25 °C was relatively low for both types of plunger materials. Even when the less preferred chlorobutyl rubber was present as the plunger material, the maximum degradation of melagatran at 25 °C was less than 5% of its starting concentration after 3 months, and was less than 10% after 6 months (table of col. 3-4). Thus, Lundgren's teaching regarding closures is limited to a preference for bromobutyl rubber over chlorobutyl rubber, and cannot be reasonably extended to provide a teaching regarding other closure materials.

Even if one of ordinary skill in the art would have overextended the teachings of Lundgren to combine them with the teachings of Zhang, the skilled artisan would have expected that the low oil propofol formulations of Zhang stored at 25 °C in a container having a closure would be somewhat more stable if the closure contained bromobutyl rubber than if the closure contained chlorobutyl rubber. This result, however, is the opposite of that reported by the inventors in Applicant's specification. In Examples 32 and 33 of Applicant's specification (pages 30-31), low oil propofol compositions were subjected to the degradation test recited in claim 1 after sealing the compositions in containers having various closures. The propofol concentrations maintained in containers having a chlorobutyl rubber closure (Rubber 4) was similar to or higher than the propofol concentrations maintained in containers having a bromobutyl rubber closure (Rubbers 1-3). As the expected results of the combination of the compositions of Zhang with the closures of Lundgren are in conflict with the results reported in Applicant's specification, any expectation of success based on the references would have been unreasonable.

One of ordinary skill in the art would not have reasonably expected success in combining the propofol compositions of Zhang with the containers of Lundgren. Lundgren's teachings regarding the storage of melagatran would not have been reasonably expected to provide stable compositions of propofol, nor would Lundgren's teachings regarding rubber materials have been extended beyond the simple selection of bromobutyl rubber over chlorobutyl rubber. Even if the references had been combined, one of ordinary skill would have expected results opposite those observed by Applicants.

As noted in MPEP 2143.02, a reasonable expectation of success is required to establish that claims are *prima facie* obvious over a combination of references. The propofol compositions of Zhang, however, could not have been combined with the containers of Lundgren with a reasonable expectation of success. Accordingly, the claims are not obvious over Zhang in view of Lundgren. Applicants request that this rejection be withdrawn.

CLAIM 1 IS NOT OBVIOUS OVER ZHANG AND SAUTOU-MIRANDA

Independent claim 1 is not obvious over Zhang in view of Sautou-Miranda. Zhang teaches away from propofol formulations such as DIPRIVAN® that include EDTA as a preservative. Sautou-Miranda teaches only a propofol formulation derived from DIPRIVAN®, and which therefore includes EDTA preservative. Thus, Zhang and Sautou-Miranda cannot be combined, as Zhang teaches away from their combination.

Zhang teaches that the metal ion chelator EDTA, which is present as a preservative in DIPRIVAN® at a level of 0.0055% (w/v), can be potentially dangerous to some patients with low calcium or other cation levels, and especially critical for ICU patients (col. 1, line 57 – col. 2, line 5; col. 2, lines 27-28). Zhang further teaches that other metal ion chelators such as pentatate present the same potential danger (col. 2, lines 6-10). The invention of Zhang is described as a "preservative-free" propofol formulation (col. 3, lines 10-13), and the elimination of preservatives is the first listed advantage of the invention (col. 3, line 27). Thus, Zhang teaches away from propofol compositions that include a

preservative, and particularly from propofol compositions that include EDTA or other metal ion chelator preservatives.

Sautou-Miranda discloses DIPRIVAN® formulations that had been diluted from their original concentration of 10 mg/ml propofol (p.252, left col., lines 1-3) to a diluted concentration of 2.5 mg/ml propofol (p.253, left col., lines 1-2). This reduced propofol concentration corresponds to 25% of the original propofol concentration. As noted in Zhang, DIPRIVAN® includes EDTA preservative at a level of 0.0055% (w/v). Thus, the diluted formulations of Sautou-Miranda would have included approximately 0.0014% (w/v) EDTA (0.0055 x 0.25).

As noted in MPEP 2145(X)(D)(2), references cannot be combined where a reference teaches away from their combination. Sautou-Miranda discloses only compositions that include EDTA preservative. Zhang teaches away from propofol compositions that include EDTA preservative. Accordingly, the claims are not obvious over Zhang in view of Sautou-Miranda. Applicants request that this rejection be withdrawn.

CLAIM 29 IS NOT OBVIOUS OVER THE CITED REFERENCES

Independent claim 29 is not obvious over Zhang in view of Lundgren and/or Sautou-Miranda. Claim 29 recites an emulsion including an oil phase that includes propofol, an aqueous phase, and a stabilizing layer for the oil phase that includes a surfactant and a protein. Zhang and Sautou-Miranda disclose propofol emulsions, but do not disclose or suggest a protein in the emulsions. Lundgren does not disclose emulsions of any sort, and thus does not disclose or suggest a stabilizing layer for an emulsion that includes a protein. Thus, the combination of the references would not provide each and every element of claim 29.

As noted above, Zhang discloses propofol formulations having a reduced amount of soybean oil triglycerides, a reduced amount of lecithin surfactant, and no preservatives (col. 3, lines 17-27). There is no disclosure or suggestion in Zhang regarding the addition of a protein to the low oil propofol formulations. As noted above, Sautou-Miranda discloses DIPRIVAN® formulations, which do not include a protein. The DIPRIVAN®

formulations are diluted with a 5% glucose mixture (p.252, left col., lines 4-5), and the reference does not disclose that this dilution mixture includes a protein. Thus, neither Zhang nor Sautou-Miranda disclose or suggest the addition of a protein to a propofol composition.

Lundgren discloses aqueous solutions of melagatran and related peptide-based thrombin inhibitors (col. 2, lines 17-18 and 65). There is no disclosure in Lundgren regarding emulsions or of any need to stabilize an oil within the aqueous solutions. Thus, Lundgren does not disclose or suggest a protein that is present in a stabilizing layer for an oil phase.

The cited references do not provide each and every element of claim 29. Zhang and Sautou-Miranda do not disclose a protein in their propofol emulsions. Lundgren does not disclose a protein in a stabilizing layer for an emulsion. Accordingly, claim 29 is not obvious over the cited references. Applicants request that this rejection be withdrawn.

CLAIM 52 IS NOT OBVIOUS OVER THE CITED REFERENCES

Independent claim 52 is not obvious over Zhang in view of Lundgren and/or Sautou-Miranda. Claim 52 recites microdroplets and an injectable carrier, where the microdroplets contain propofol spheres surrounded by a layer that includes a phospholipid but that does not include an oil that can support bacterial growth. Zhang and Sautou-Miranda disclose propofol emulsions that include soybean oil, which supports bacterial growth. Lundgren does not disclose emulsions, including microdroplet emulsions. Thus, the combination of the references would not provide each and every element of claim 52.

Zhang requires that propofol be dissolved in a water-immiscible solvent, which may be a vegetable oil and preferably is soybean oil (col. 3, lines 62-66; col. 4, lines 31-46). Soybean oil supports bacterial growth, even at reduced concentrations of 2-3% (Zhang, col. 2, lines 43-49). While Zhang discloses propofol formulations having a reduced amount of soybean oil relative to DIPRIVAN®, the minimum concentration of water-immiscible solvent disclosed is 3% by weight (col. 4, lines 18-23). There is no disclosure or suggestion in Zhang that soybean oil or a similar substance can be absent from the

formulations. Thus, Zhang discloses only propofol formulations that contain an oil that can support bacterial growth.

Sautou-Miranda discloses only DIPRIVAN® and diluted compositions of DIPRIVAN®. DIPRIVAN® contains 10% (w/v) soybean oil (Zhang, col. 1, lines 57-60). Thus, Sautou-Miranda discloses only propofol formulations that contain an oil that can support bacterial growth.

Lundgren discloses aqueous solutions of melagatran and related peptide-based thrombin inhibitors, as noted above. There is no disclosure in Lundgren regarding microdroplets of oil within the aqueous solutions or other injectable carrier. Thus, Lundgren does not disclose or suggest microdroplets surrounded by a layer that includes a phospholipid but that does not include an oil that can support bacterial growth.

The cited references do not provide each and every element of claim 52. Zhang and Sautou-Miranda do not disclose propofol compositions having microdroplets containing propofol without an oil that can support bacterial growth. Lundgren does not disclose microdroplets in an injectable carrier. Accordingly, claim 52 is not obvious over the cited references. Applicants request that this rejection be withdrawn.

CONCLUSION

Upon the indication of allowable subject matter, the Examiner is respectfully requested to telephone Jonathan P. Taylor at (312) 612-6700 to resolve any outstanding issues as expeditiously as possible so the case may be passed to issue.

Respectfully Submitted,

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Date

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